Adenocarcinoma of the cervix uteri; does it really carry a worse prognosis? A single institutional review from Egypt

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ABSTRACT

Background: Cervical uteri carcinoma is 4th commonest cancer affecting women worldwide. Its incidence is increasing in developing countries being 2nd commonest cancer & 3rd cause of cancer mortality. Although incidence of squamous cell carcinoma (SCC) is declining in developed areas, adenocarcinoma (AC) is proportionally rising despite effective screening. AC cases are younger, usually whites, diagnosed early with frequent nodal disease. Prognostic parameters for AC include; stage, age, depth of invasion, treatment given, DNA ploidy, S-phase fraction, architectural & nuclear grading, involved LNs and repeated HPV infection especially 16, 18 & 45. Early disease is frequently asymptomatic with nonspecific presentations usually mistaken for simple cervicitis. With disease progression; pelvic or lower back pain, GIT or urinary symptoms appears. Treatment is tailored according to stage, age & PS. Early cases are treated either with surgery or concurrent chemo-radiation (CCRT). *Aims:* to study clinicopathological features of all cases of AC of the cervical uteri, diagnostic tools, management protocols & outcome. *Materials & Methods*: A single institution prospective analysis of all cases presented to NCI-Cairo University with AC of the cervix uteri candidate for surgery over a period of 4 years from October 2015 to October 2019. 37 cases were included. Data collected from patients archives then analyzed. *Results:* Mean age was 54 years ranging (15-80 year). 36 cases were married (~97%). Vaginal bleeding encountered in (33 cases, ~89%). 22 cases (~59%) were post-menopausal. Three cases had positive family history in three cases (~8%). Punch biopsy was done for (26 cases, ~70%). 17 cases (~46%) performed CT only as diagnostic tool. Mucinous subtype occurred in (21 cases, ~ 57%). Grade II found in (14 cases, ~38%). Stage II-b predominated (11cases, ~30%). Preoperative treatment was given to (28 cases, ~ 76%). Surgery was done for (23 cases, ~62%) via open approach (18 cases, ~49%), robotic radical hysterectomy for (2 cases, ~5%) only while (3 cases, ~8%) underwent anterior pelvic exenteration. Postoperative stay ranged (5-32 days) with median 11 days. Commonest complication was surgical site infection (SSI) (13 cases, ~35%). 5 cases (13.5%) showed positive surgical margins. Positive pathological LNs after resection was found in (6 cases, ~16%) while no residual pathology was found in only 2 cases. Adjuvant treatment was needed in (14

cases, ~38%). *Conclusion*: AC patients experienced worse overall survival & disease-free survival than their counterpart SCC regardless treatment with RT or CCRT. Surgery is the primary treatment only for very early stages (I-a). In advanced tumors neoadjuvant or definitive CCRT is the role saving surgery for salvage. Fast recovery with early discharge & less complication are noticed with minimally invasive techniques. Novel protocols should be introduced to improve outcomes of locally advanced & metastatic patients.

Keywords: Adenocarcinoma, Cervix, Prognosis, NCI, EGYPT

1. INTRODUCTION

Carcinoma of the cervix uteri is the 4th cancer worldwide after breast, colorectal & lung carcinomas constituting 8.8% of female cancer & 20.9% of gynecological cancer in USA. 13,240 new cases & 4170 deaths were identified in USA only in 2018. It is the 4[th]among cancer related mortalities worldwide, while in Africa & Central America it is the leading cause of cancer-related mortality (Ferlay et al., 2013). The incidence is increasing in developing countries being 2nd commonest cancer (15.7 per 100,000 women) & 3rd cause of cancer related mortality (8.3 per 100,000) where screening programs may not be so effective. A major risk factor for its carcinogenesis is Human papillomavirus (HPV) causing genetic structural & function alteration, others include; smoking, immunodeficiency, oral contraceptives, high parity, smoking, HIV & other STDs (Wright et al., 2013). Two main types exist, squamous cell carcinoma (SCC) (69%) & adenocarcinoma (AC) (25%) with different oncogenic mutations & immunologic tumor microenvironment. Otherr are types [<6%] include (adenoid cystic, neuroendocrine, mixed epithelial-mesenchymal tumors & undifferentiated carcinoma). Although incidence of SCC is declining in developed countries, AC shows alarming proportional rise despite effective screening programs. This may be due to the fact that progression toin-situ AC & invasive AC from low grade or high-grade lesions are not well established in AC on the contrary of its counterpart SCC (Siegel et al., 2018; Sasieni et al., 2009).

AC is staged according to the joint 2010 International Federation of Gynecology and Obstetrics (FIGO)/TNM classification system for cervical carcinoma. Prognostic parameters for AC include stage, age, depth of invasion, treatments given, size, DNA ploidy, S-phase fraction, architectural & nuclear grading, LNs status and repeated HPV infection especially types 16, 18 & 45. Histo-pathologically; two main types of AC exist (mucinous & endometrioid). Clinically, patients tend to be younger with peak at 45 years, white race, early diagnosed & frequently have metastatic nodal disease (Galic et al., 2012). Early disease is asymptomatic & usually discovered incidentally (20% of patients) on screening orroutine pelvic examination. Commonest presentations include irregular or heavy vaginal bleeding, post-coital bleeding, vaginal discharge that may be watery, mucoid, purulent & malodorous which is a nonspecific finding & usually mistaken for simple vaginitis or cervicitis (deFreitas et al., 2012). With disease advancement, patients suffer pelvic or lower back pain radiating posteriorly along lower extremities, GIT or urinary symptoms (diarrhea, stress incontinence, deep pelvic heaviness, hematuria, hematochezia, vesicovaginal or rectovaginal fistula) (DiSaia and Creasman, 2007).

Physical examination is usually normal in early AC, with disease progression, exophytic or endophytic lesions appear with the specific bloody purulent discharge. A high index ofsuspicion withearly diagnosis should be achieved histo-pathologically & radiologically. This is done through proper colposcopic examination & biopsy (punch or endocervical curettage) together with Transvaginal US, CT, MRI or PET-CT either for the 1[ry] disease or when suspected recurrence (Hricak et al., 2007). Despite different pathological types for cervical carcinoma, treatment options are the same. It is tailored according to stage, age & performance status (PS). Early stages are treated either with radical hysterectomy (total abdominal hysterectomy & pelvic lymphadenectomy) or definitive concomitant chemoradiation (CCRT) with equivalent survival outcomes (DFS & OS) to its counterpart SCC. For locally advanced cases, the standard management is CCRT (Xie et al., 2018). In selected patients with very early disease, cervical conization or simple hysterectomy only can be an option. Bevacizumab is one of molecular targeted agents addressed in several studies for its role in recurrent or metastatic disease and was well tolerated & active in 2nd& 3rd lines of treatment for cases with treatment failures (Jung et al., 2017). Poor radiosensitivity of AC is one of the causes of its worse survival than SCC. It is the reason for increased local recurrence & systemic failure rates after RT or CCRT. AC patients do not suffer poorer complete response (CR) only but requires longer time to achieve this CR after RT or CCRT. With introduction of CTH agents, this survival difference between AC & SCC showed significant decline (Yokoi et al., 2017).

Currently, cisplatin is the most favorable drug for SCC. However, it may not be appropriate with AC. Some studies indicated that paclitaxel instead is an active agent for AC. Huang et al. Reported that; AC/SCC patients with advanced stage or L. Ns involvement showed 5-years DFS rates with RT alone (41.7%), cisplatin-based CCRT (41.7%) & paclitaxel-based CCRT (53.8%) [p=0.611] denoting that paclitaxel-based formulas carried a better DFS than cisplatin based regimen or radiation alone (Curtin et al., 2001). Considering poor survival of AC, effective neoadjuvant chemotherapy with the adjuvant protocols is intensively needed. In a trial from China, 880

patients with stages IIB-IVA were randomized to receive either CCRT or CCRT with single cycle of neoadjuvant chemotherapy+2 cycles of consolidation chemotherapy. Drugs for neoadjuvant & consolidation chemotherapy were paclitaxel +cisplatin. After median follow-up period of 60 months, patients in CCRT arm combined with neoadjuvant & adjuvant chemotherapy experienced better DFS($p < 0.05$), OS (< 0.05) & local control rates ($p < 0.05$) suggesting that incorporating neoadjuvant & adjuvant chemotherapy to CCRT is a promising approach for survival improvement of AC patients (Tang et al., 2012).

Aim of work

This cohort aimed to study to study clinicopathological features of all cases with AC of cervix uteri, management protocols, surgery, complications, radiation, chemotherapy given & outcome of treatments 'DFS'& 'OS'.

2. PATIENTS AND METHODS

A prospective descriptive analysis of all patients diagnosed with AC of the cervix uteri & treated at National Cancer Institute, Cairo University, Egypt from October 2015 to October 2019. 37 patients were included. Data collected then analyzed. Data included (name, age, comorbidities, date of first visit, performance status, family history, menopausal status, marital status, number of offspring's, presentation, histopathology, grade, stage, neoadjuvant treatment, surgery, postoperative complications, adjuvant treatment & outcome (OS, DFS).

Statistical methods

Data management & statistical analysis performed using Statistical Package for Social Sciences (SPSS) vs. 21 (SPSS Inc., Chicago, IL). Numerical data presented using means & standard deviations or medians & ranges. Categorical data were presented as percentages. Kaplan & Meier procedure was used to estimate overall survival (OS) & disease-free survival (DFS) rates. Comparisons between different prognostic factors were done using Logrank test.

3. RESULTS

37 patients were included with cervical adenocarcinoma; ages ranged from 15 to 80 years (median; 54years). 22 patients (59.5 %) were post- menopausal (table 1).

Table 1 Patients characteristic (37 cases, 100%)		
Age (years)	Mean age was 54 years ranging (15-80 y)	
Marital status	Single	1 case, 2.7%
	Married	36 cases, 97.3%
No. of offspring	Median 4(range1-8)	
Menopausal status	Postmenopausal	22 cases, 59.5%
	Premenopausal	15 cases, 40.5%
Family history	Negative	34 cases, 91.8%
	Positive	3 cases, 8.2%
Co-morbidity	DM	9 cases, 24.3%
	HTN	28 cases, 75.7%
Performance status	I	28 cases, 75.6%
	II	7 cases, 18.9%
	III	1 case, 2.7%
	IV	1 case, 2.7%
Presenting symptoms	Bleeding	30 cases, 81.1%
	Pelvic pain	4 cases, 10.8%
	Vaginal discharge	3 cases, 8.1%
Main radiological investigation: Initial	CT	17 cases, 45.9%
	TVUS	9 cases, 24.3%
	MRI	11 cases, 29.8%
Recurrence	FDG PET CT (recurrence)	8 cases, 21.6%

	Punch bx	26 cases, 70.3%
Pathological diagnosis	Endocervical curettage	11 cases, 29.7%
Histological variant:	Mucinous	21 cases, 56.8%
	Endometrioid	8 cases, 21.6%
	Serous	5 cases, 13.5%
	Papillary	3 cases, 8.1%

Postoperative stay ranged (5-32 days) with median of 11 days. The benefit of fast recovery & discharge with less postoperative complication was with (2 cases, 5.4%) underwent robotic radical hysterectomy (both were discharged after 5 days). Delay from first presentation until surgery ranged (11- 90 days) with median 29 days. Negative margins either distal vaginal or lateral parametrial were obtained in (18 cases, 48.6%), of the (23 cases, 62.1%) underwent surgery; only 5 cases (13.5%) showed positive margins.

Commonest postoperative complication was surgical site infection (SSI) (13 cases, 35.1%). Incisional hernia in (3 cases, 8.1%), ureteric injury in (1 case, 2.7%) where it underwent primary repair with insertion of double J stent for 4 weeks, vesico-vaginal fistula in (2 cases, 5.4%) managed conservatively until spontaneous closure after 3 months. DVT occurred in (2 cases, 5.4%). On long term follow-up hydronephrosis occurred in the patient (2.7%) with previous ureteric injury & managed with ureteroscopic balloon dilatation & stenting again (table 2-3 & figure 1-3).

| Table 2 Stages of the disease &Modalities of treatment		
Stages: Stage I-b1 Stage I-b2 Stage II-a Stage II-b Stage III-a Stage III-b Stage IV-a Stage IV-b	2 patients, 5.4% 7 cases, 18.9% 3 cases, 8.1% 11cases, 29.7% 5 cases, 13.5% 3cases, 8.1% 2 cases, 5.4% 4 cases, 10.8%	
Preoperative treatment (28 cases, 75.6%)	Type: CCRT CTH RTH	22 cases ,9.4% 4 cases, 10.8% 2 cases, 5.4%
	Response: Complete Remission (CR) Progressive Disease (PD) Regressive Disease (RD) Stable Disease (SD)	10 cases, 27% 4 cases, 10.8 % 13 cases, 35.1% 1 case, 2.7%
Surgery (23 Cases, 62.1%)	Open Robotic Anterior pelvic exenteration	18 cases, 54% 2 cases, 5.4% 3 cases, 8.1%
Postoperative Pathology (23 Cases, 62.1%)	Grading: II III NA	14 cases, 37.8% 7 cases, 18.9% 2 cases, 5.4%
Lns Metastasis (23Cases, 62.1%)	Involved	6 cases, 16.2%
	Free	17 cases, 45.9%
Resection Margin (23Cases, 62.1%)	Negative	18 cases, 48.6%
	Positive	5 cases, 13.5%
Adjuvant Treatment (14Cases,	CCRT	5 cases, 13.5%

37.8%)	RT	9 cases, 24.3%

Table 3 Patterns of failure in our study (37 cases, 100%)		
Site	Yes	12 cases, 32.4%
	Locoregional	3 cases, 8.1%
	Distant	4 cases, 10.8%
	Both	5 cases, 13.5%
Treatment	CTH only	9 cases, 24.3%
	CCRT	2 cases, 5.4%
	Surgery (salvage/ palliative)	3 cases, 8.1%
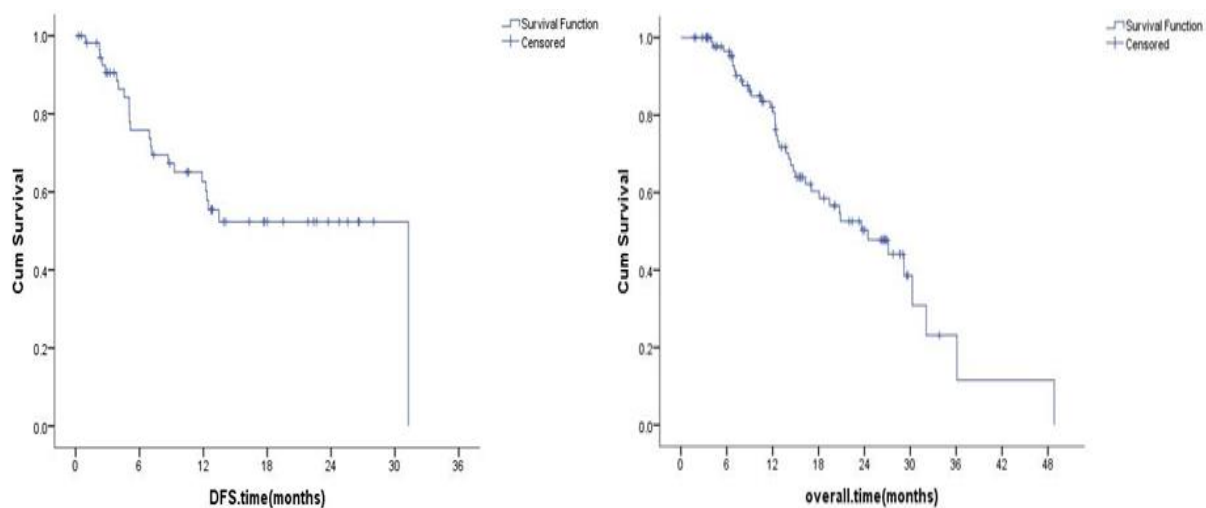
Figure 1 DFS (left) & OS curves (right) in our cohort

The median follow-up period in our work was 29.7 months (ranging 8.3–63.3 months) (p-value < 0.05). The 3-year OS was 63.4% & DFS was 47.6%. The pelvic control rates & distant control rates were 54.3% & 61.4% respectively (p-value <0.05).
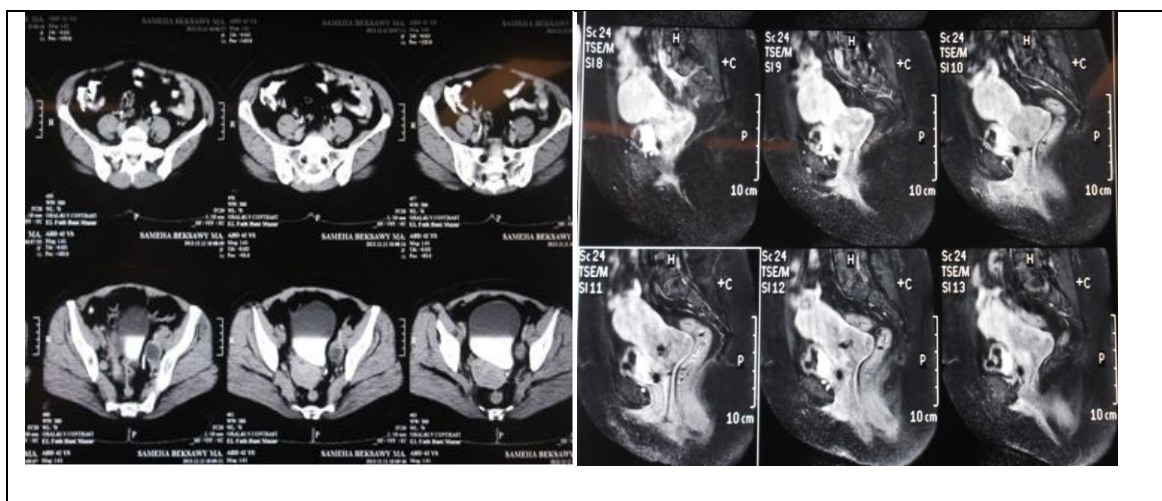
Figure 2 CT (axial view) showing enlarged cervix with protruding mass (Left.) & MRI (sagittal view) of another patient showing again a cervical mass bulging to vagina (Right)
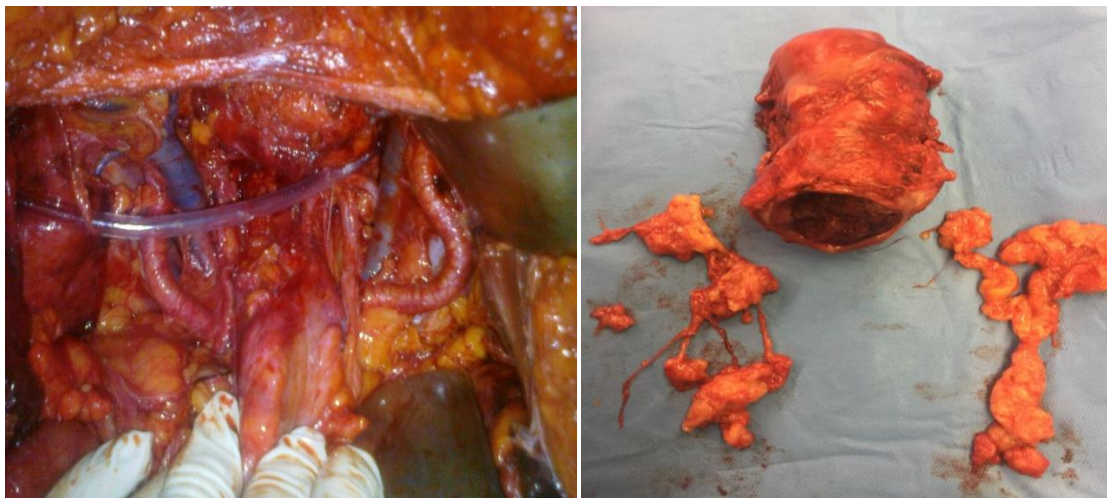
Figure 3 Intraoperative view showing operative field after Wertheim operation (left) & post-operative specimen showing of Wertheim operation (Right).

4. DISCUSSION

In Egypt, according to WHO; 866 women are diagnosed annually with cervical AC & 373 women dies from it each year. It ranks the 13th cancer among Egyptians & 10thcancer between 15-44 years. It represents 1.9% of all female cancers (Ibrahim et al., 2014; Torre et al., 2015). As a result of implementation of screening & HPV vaccines, SCC incidence significantly decreased in developed countries. Despite this, incidence of AC shows continuous rise with worse prognosis & dismal survival. The AC rates had risen from 0.5% to 3% per year in Europe compared to SCC. This may be due to the ineffective & deceiving free results of cytological screening for AC (Watson et al., 2008). About 20% of patients are asymptomatic. Early cases may be mistaken as chronic cervicitis. With disease advancement, prompt presentations usually appear. In our cohort vaginal bleeding (either spontaneous or postcoital) was the most alarming symptom (33 cases, 89.1%) that brought our patients to clinics followed by pelvic pain (4 cases, 10.8%) then discharge (3 cases, 8.1%). Almost all our cases were married (36 cases, 97.3%) & were postmenopausal (22 cases, 59.5%) that may carry the risk for repeated & chronic HPV infections (Noh et al., 2014).

Screening is achieved by Papanicolaou test, HPV testing or co-testing of the partner who is usually initiated at age of 21 years in asymptomatic sexually active immunocompetent ladies. In our work in NCI there was no screening programs initiated until this cohort is published, however; the Ministry of Health is implementing a national screening program for cervical carcinoma in EGYPT that will start by the year 2022 (Denny et al., 2013). A problem commonly faced clinically is with those lesions involving the lower uterine segment & upper endocervix. The primary origin of this adenocarcinoma is extremely an important as treatment strategies are different for endometrial and cervical AC. This issue could be solved by IHC markers staining where typical endocervical AC are (ER, PR & Vimentin negative-CEA positive) while typical endometrial AC tends to be (ER, PR & Vimentin positive; CEA negative) (Alkushi et al., 2003). Although two main histological types of endocervical AC exists (mucinous & endometroid), other rare types actually occur (serous, papillary & villoglandular). Most authors claim that this histological subtyping has no prognostic impact on survival. However, in a study by Saigo et al. found that endometrioid type showed better prognosis compared to other subtypes. Other studies concluded that the papillary (villoglandular) type was the best concerning prognosis (Saigo et al., 1986; Collinet et al., 1999).

In this work study most of our cases were of the mucinous type (21 cases, 56.8%) with no significance of the histological variant on survival outcomes was found. Although this we made a conclusion from our data that the endometrioid subtype cases carried worse prognosis as all were diagnosed as locally advanced (stage III-a & III-b) (8 cases, 21.6%), while the serous type (5cases, 13.5%) & the villoglandular (3 cases, 8.1%) subtypes carried a more favorable outcome as they were diagnosed less advanced (I-b and II-b). Treatment of cervical AC is stage adjusted. In very early disease (stage I-a1) without lympho-vascular space invasion (LVSI), fertility-sparing conization with negative margins is enough. If margins are still positive, conization is repeated or trachelectomy is done. When fertility is not a relevant issue, simple hysterectomy is offered. When LVSI exists, same procedures are done pluspelvic Lymph Nodes (LN) dissection+/-paraaortic LNs sampling (may consider sentinel LNs mapping) (Winer et al., 2015).

For stage I-a 2, options include Fertility-sparing radical trachelectomy & pelvic LNs dissection with watchful waiting if margins & LNs were negative. For patients not desiring fertility; pelvic Radiation+brachytherapy or brachytherapy alone is a safe option. When there is LVSI; radical trachelectomy or modified radical hysterectomy+ pelvic LNs dissection, or radical hysterectomy +LNs dissection is offered. In our study, there were no cases presented with stage I-a disease either I-a1 or I-a2 representing a defect in early presentation of Egyptian females (Kokka et al., 2014). Stage I-b1 management includes fertility-sparing (radical trachelectomy+ pelvic LNs dissection for tumors ≤2 cm or radical trachelectomy/conization + pelvic LNs dissection) +/-CTH. Non fertility-sparing options include (radical hysterectomy plus pelvic LNs dissection or pelvic RT & brachytherapy +/-concurrent paclitaxel-based CTH. In this cohort two cases (5.4%) presented with stage I-b1; one case (2.7%) underwent CCRT & achieved complete pathological complete remission (CR), the other(2.7%) showed stationary course where it was offered Wertheim's operation (Li et al., 2013).

For stage I-b2; CCRT or radical hysterectomy+pelvic LNs dissection is the role. In this cohort (7cases, 18.9%) presented with stage I-b2; (5 cases, 13.5%) underwent Wertheim operation & (2 cases, 5.4%) received CCRT one of them (2.7%) achieved CR while the other (2.7%) showed partial regression (PR) where she was offered Wertheim operation (Marie et al., 2017). Stage II-a treatment includes CCRT, radical hysterectomy+pelvic LNs dissection or pelvic radiation+ brachytherapy +/-concurrent paclitaxel-based chemotherapy. In our work (3 cases, 8.1%) presented with stage II-a; (2 cases, 5.4%) received neoadjuvant CCRT & showed progressive disease (PD) where they underwent Wertheim operation. One of these patients (2.7%) developed local recurrence 6 months later. The remaining case (2.7%) underwent upfront Wertheim operation & developed local recurrence after 4 months (Landoni et al., 2014). For stage II-b treatment is CCRT + brachytherapy. In our study, this was the most common stage (11cases, 29.7%). All 11 cases received neoadjuvant CCRT; 5 showed CR (13.5%) one of them (2.7%) developed locoregional recurrence within six months, (5cases, 13.5%) showed regression and then underwent Wertheim operation while one case (2.7%) showed progression on treatment where it was offered palliation (Landoni et al., 2014; Trifiletti et al.,2015).

Locally advanced stages III-a, III-b & stage IV-a treatment is CCRT + brachytherapy. In our study, (5 cases, 13.5%) presented as stage III-a & (3 cases, 8.1%) as stage III-b & (2 cases, 5.4%) as stage IV-a. 8 cases (21.6%) received neoadjuvant CCRT, (3 cases, 8.1%) showed CR.5 cases (13.5%) experienced PR. The two cases (5.4%) presented with stage IV-a underwent palliative RT only with initial partial regression then progressed after two months where they were offered palliative CTH (Duenas-Gonzalez et al., 2011). According to our cohort, It seems that starting from stage II disease which is considered an early stage in SCC, the incidence of local recurrence & systemic failure rises in AC patients representing a really dramatic poor prognosis and may offer the need formore intense systemic therapy protocols as early as stage II disease and even for more earlier stages as stage I (Landoni et al., 2014; Trifiletti et al., 2015; Duenas-Gonzalez et al., 2011).

For stage IV-b treatment (4cases, 10.8%) in our work, Chemotherapy is given on a palliative basis; cisplatin-based combination was first line. Second line includes docetaxel, gemcitabine, ifosfamide, irinotecan & t opotecan. RT may be considered as a palliation for control of bleeding and pain (Monk et al., 2010). Robotic & laparoscopic approaches are now usedmore frequently & have been found therapeutically feasible & beneficial. Wang et al. reported that oncologic outcomes post minimally invasive radical hysterectomy procedures are comparable to the usual open approaches after 3-6 years of follow up. In this study only (2 cases, 5.4%) underwent robotic Wertheim operation, both showed very smooth post-operative course, rapid recovery & short stay (both were discharged after 5 days) (Wang et al., 2015).

During follow-up (12cases, 32.4%) suffered recurrence either locoregional or systemic. Treatment depends on its site & previous treatment. For locoregional recurrence without previous RT, surgery if feasible or Radiation+/- CTH or brachytherapy is offered. In this work (3 cases, 8.1%) developed locoregional recurrence [2 post Wertheim (5.4%) treated with CCRT & one post primary definitive CCRT (2.7%) treated with salvage anterior pelvic exenteration]. Patients suffering central recurrent lesions with previous RT are treated with either pelvic exenteration +/- intraoperative RT. Radical hysterectomy or brachytherapy can be offered only for recurrences <2cm. Those with non-central lesions are treated with either EBRT +/- CTH, surgery +/- RT, CTH alone or just best supportive care (Duenas-Gonzalez et al., 2011; Monk et al., 2010; Nagao et al., 2005). For distant metastasis, management would be with either CTH or best supportive care. Four cases (10.8%) developed distant metastasis post Wertheim (onein lungs, one in bones, one in liver and last one in peritoneum with malignant ascites); all were treated with single agent CTH (Nagao et al., 2005).

In our work, five cases (13.5%) developed both locoregional & distant failure (three in lungs, one in bone, the last one in bone & liver) post Wertheim; all were managed again with single agent CTH. Palliative anterior pelvic exenteration was done for (two cases, 5.4%) with disease failure (both local & systemic) suffering malignant vesicovaginal fistula with good performance status (PS). Patients with AC present more with para-aortic LNs, experienced more local failure, more likely to have distant failure & had worse survival, compared with SCC. In a study conducted by Ke Hu et al. comparing SCC & AC, the 3-years OS rates were 85.4 and 75.4%, respectively (p = 0.005), and the 3-years DFS was 77.5 and 57.3%, respectively (p < 0.001). With multivariate analysis, AC was an

independent prognostic factor of OS (p = 0.003) and DFS (p < 0.001). In this work, the risk of relapse or metastasis (DFS) was 2.4 times more for advanced stages III, IV than stages I & II & was three times more for grade III than grade I tumors (Ke Hu et al., 2018).

The current study showed prognostic significance only with disease stage where the 3 years DFS for stage I was (79.7%), stage II was (64.2%) which dropped to (30.1%) for stage III (p-value <0.05). Again, the OS for stage I was (86.4%), stage II was (72.4%) which dropped with stage III to 41.8% (p-value <0.05). Our median follows up period was 29.7 months (ranging 8.3–63.3 months) (p-value < 0.05). The overall 3-year OS was 63.4% & DFS was 47.6%. The pelvic control rates & distant control rates were 54.3% & 61.4% respectively (p-value <0.05). The risk of death (OS) was 6.71 times more for grade III than grade I and was 57% less among those received CCRT than who did not.

Sentinel lymph node mapping (SLNM) has high sensitivity & detection rate in early stages diminishing risks of neurovascular injuries, blood loss, bacterial infection & lymphedema as most of our cases was advanced with evident of affected pelvic LNs, there was so no role for SLNM (Diab, 2017). Targeted therapies as Bevacizumab + CTH are now considered the 1ˢᵗ line treatment for recurrent or metastatic cases with significant impact on OS as shown by Tewari et al. (2014). Again, Image guided adaptive brachytherapy (IGABT) combined with CCRT led to improved clinical outcome compared to 2D brachytherapy. Although this, protocols are not implemented as a standard management for locally advanced cases in our institution (Tanderup et al., 2016).

5. CONCLUSION

AC patients experienced worse overall survival & disease-free survival than their counterpart SCC regardless treatment with RT or CCRT. Surgery is the primary treatment only for very early stages (I-a). In advanced tumors neoadjuvant or definitive CCRT is the role saving surgery for salvage. Fast recovery with early discharge & less complication is noticed with minimally invasive techniques. Novel protocols should be introduced to improve outcomes of locally advanced & metastatic patients.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of National Cancer Institute/Cairo University.

Data and materials availability

All data associated with this study are present in the paper.

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